



ECP Bone Workshop

Day 2, Session 1

Validation of Exercise Countermeasures

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The thesis of this session of the ECP Bone workshop is that computer modeling is required in order to evaluate factor of risk for fracture when considering the uniquely localized bone loss conditions experienced by Astronauts. This session provides an opportunity to introduce the Integrated Medical Model Bone Fracture Risk (IMM-BFxRM) simulation approach and how this and other models improve understanding of the effects of exercise countermeasures. This workshop session also provides an opportunity for the panel to provide recommendations on this and other “complex modeling” approaches, as well as, the importance of funding the IMM-BFxRM and companion efforts by external scientists (Lang and Keyak).



ECP Bone Workshop Day 2, Session 1 Validation of Exercise Countermeasures

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Validating ECM's

- We've Heard that ECM's appear to attenuate loss in BMD in ground-based evaluations
 - Supported by DXA BMD measurements
- However –
 - Biomarkers for Bone resorption continue to be elevated
- Possible Implications
 - Exercise is stimulating bone formation only
 - Exercise is not inhibiting elevated bone resorption
 - Bone resorption biomarkers are not sensitive enough to detect positive, site-specific effects of ECM
- Focus
 - How do we go about validating the ECM application?



Bone Quality

- NIH - “The sum total of characteristics of the bone that influence the bone’s resistance to fracture” and Whole Bone Strength
 - Fyhrie DP (2005) Summary—Measuring “bone quality.” J Musculoskelet Neuronal Interact 5:318–320.
- “...the concept of bone quality is invoked to explain fracture risk that cannot be attributed to BMD.” and we lack “... criteria for defining good and bad bone quality”
 - Sievänen H (2007) “Bone Quality : An empty Term.” PLoS Medicine 4:3:407-410
- Changes in bone quality can affect:
 - bone stiffness and strength, toughness or resistance of bone to fracture, damage content, susceptibility and tolerance
 - Mitch Schaffler



Bone Quality cont.

- Contributors Include
 - BMD (Mass)
 - Geometry and Spatial Distribution of the Bone Mass
 - Microarchitecture
 - Intrinsic Bone Material Properties
 - Bone Remodeling
 - Rate, activation frequency
 - Influences all the above contributors
 - Other “Bone” Factors
 - Genetic Profile
 - Loading conditions
- Assessment Tools
 - BMD
 - DXA & CT
 - Microarchitecture
 - Novel Ultrasound
 - μ CT and μ MRI
 - Mineralization
 - CT and μ CT
 - Organic composition
 - In situ Raman spectroscopy?
 - Damage state
 - None except tissue

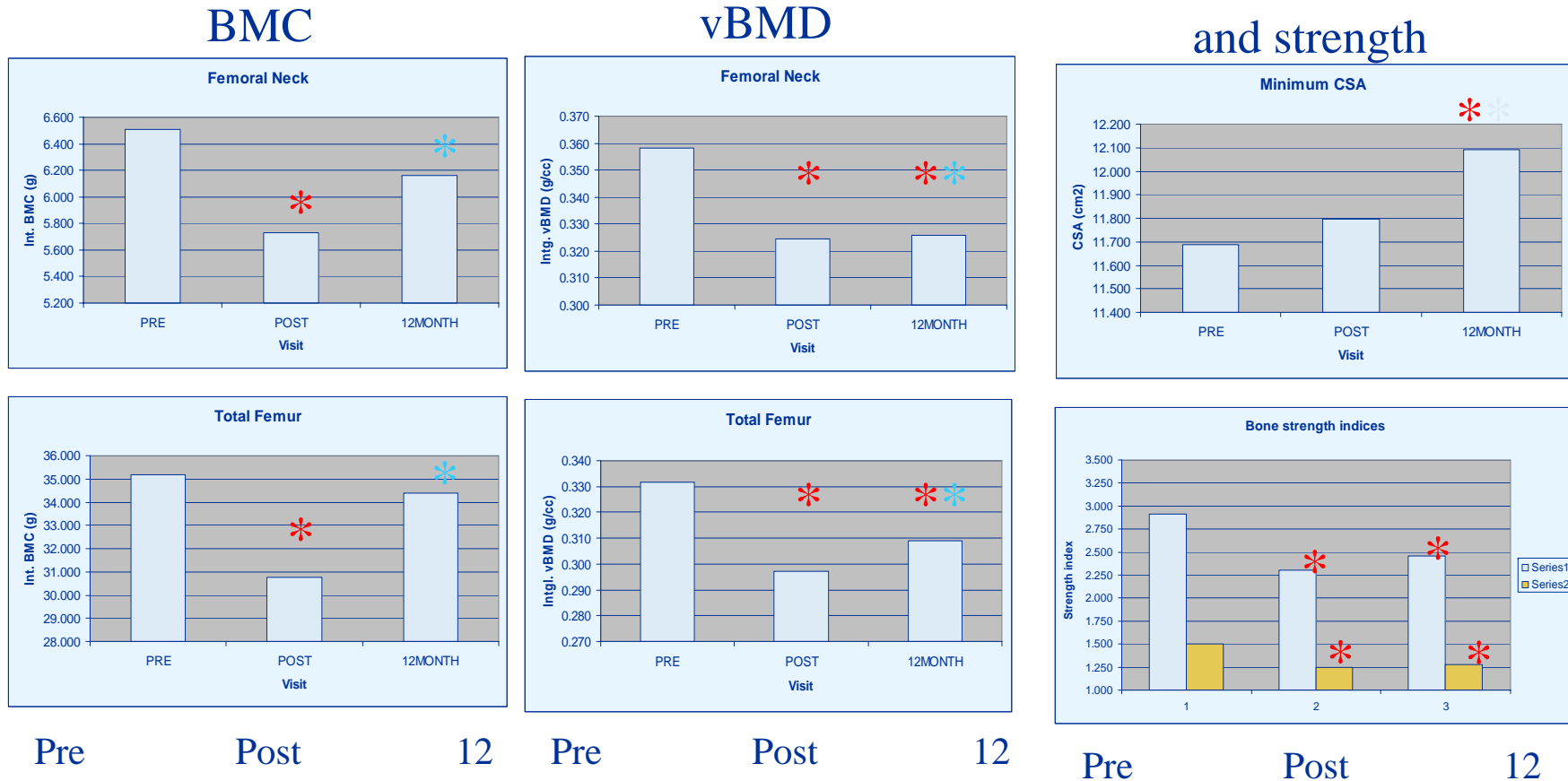
Guidance on this list from Mitch Schaffler



Femoral Neck Changes Due to Space Flight

T. Lang et al., JBMR 2006.

Minimum FN CSA and strength



* *: p < 0.05 with respect to preflight, postflight

□ bending (cm³)
 ■ compressive (g²/cm⁴)



Perspective on Strength Loss

- Comparison using data from
 - Cross-sectional study of Caucasian women
 - 128 elderly (70 - 80yr)
 - 30 pre-menopausal (35 - 45yr)
 - 11 astronauts post flight
- Method: CT Image based, FEM element modeling for stance and fall loading conditions
- Change in Estimated Bone Strength:

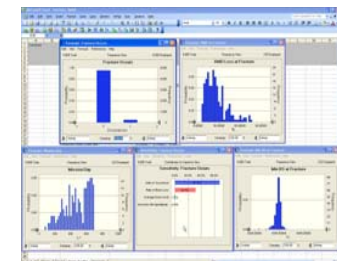
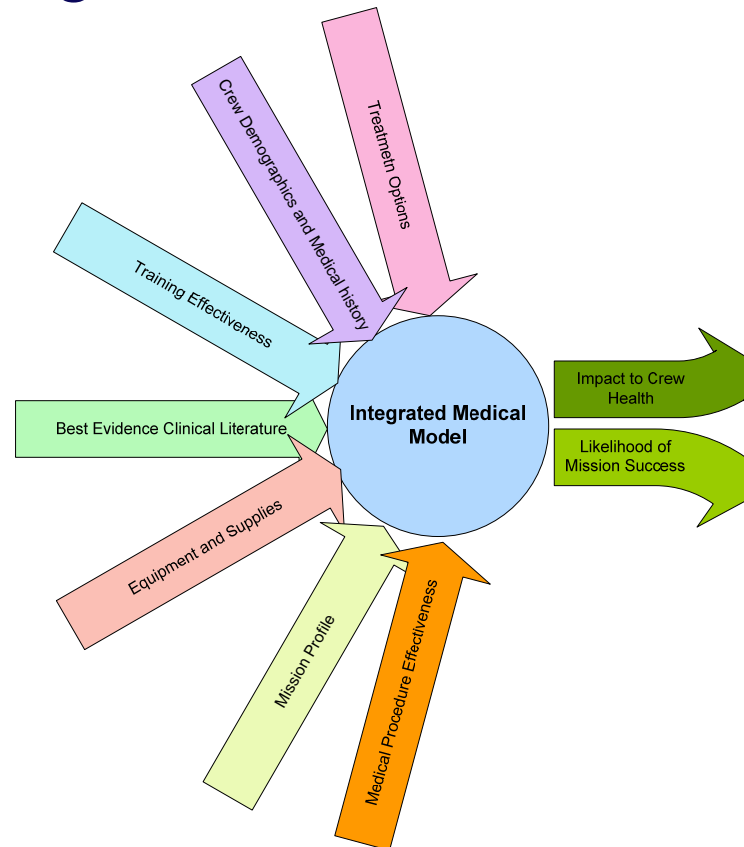
	Lifetime loss due to aging, mean	6 mo in space, median (range)
Stance	6.9%	13% (4 to 30%)
Fall	24.4%	14% (0 to 23%)

Keyak et al, ()



Integrated Medical Model

Potential Medical Condition



Likelihood of occurrence, probable severity of occurrence, and optimization of treatment and resources.

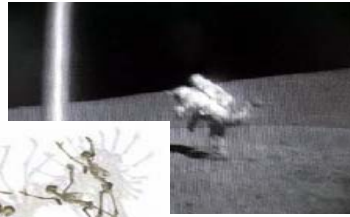
- The Integrated Medical Model (IMM) is a tool for quantifying the probability and consequences of medical risks
- Integrate best evidence in a quantifiable assessment of risk
- Identify medical resources such as skills, equipment, and supplies necessary to optimize mitigation strategies.



Modeling Fracture Potential For Exploration Missions Integrated Medical Model - Bone Fracture Risk Module

Bone Fracture is a multi-factorial problem that includes both intra-skeletal and extra-skeletal factors

**Biomechanics
and Mission
Operations**



courses.washington.edu/me598rc

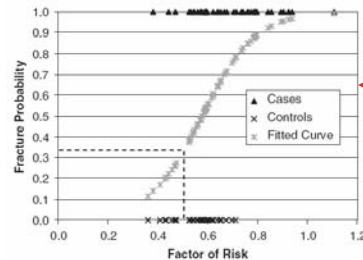
**Bone Loss in
Space**



**Estimate of
Fracture Probability**

$$FRI = \frac{\text{Applied Load}}{\text{Bone Strength}}$$

**Appropriate
Metrics and
Evidence-Based
Conversions to
Probability**



**Clinical and
Engineering
Characteristics of
Bone Strength**

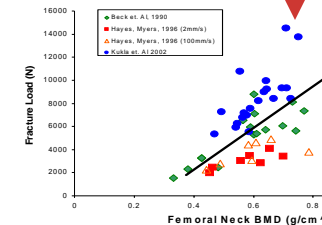


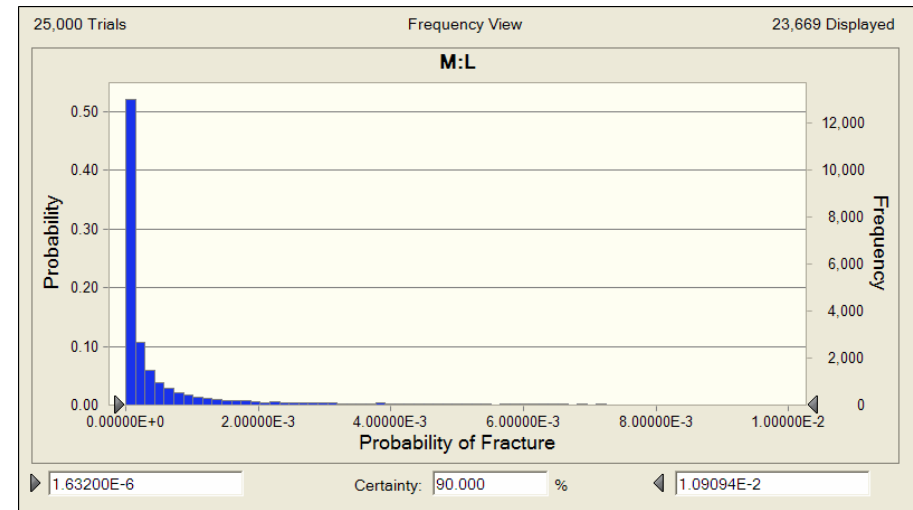
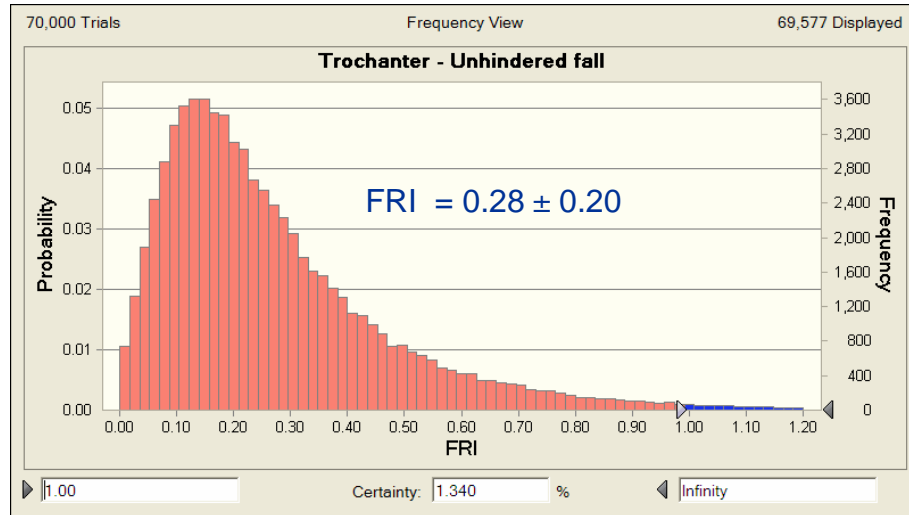
Figure 2. Summary of literature survey on fracture load as a function of femoral neck BMD





Probability of Fracture Due to Side Falls Male on Extra Vehicular Activity

•Data Shown for Mars: 540D Surface Mission



Mission	Fracture Prob	Std	5th Percentile	95th Percentile
Lunar: 8D Surface	1.50E-4	1.15E-3	3.30E-07	5.36E-04
Lunar: 170D Surface	1.94E-4	1.54E-3	3.47E-07	6.15E-04
Mars: 40D Surface	1.44E-3	7.66E-3	1.15E-06	4.85E-03
Mars: 540D Surface	2.47E-3	9.95E-3	1.68E-06	1.15E-02

- Lateral/Posteriolateral Fall heights range from .25m to ~1m
- Bone loss not attenuated by partial gravity



Discussion Questions

- What biological endpoints need to be monitored/evaluated in order to validate exercise countermeasures?
 - Are 'biometrics' instrumentation or sensors to quantify loading histories (time rate of change, magnitudes, frequencies) needed?
- How is bone loss being “attenuated” by exercise in reported bed rest studies?
 - Are we suppressing bone loss or are we building bone?
 - Is it important to make this distinction?
- Can we justify taking bone biopsies in test subjects or crew members to evaluate cellular/tissue responses or should we rely on animal studies?



Discussion Questions (2)

- How do we evaluate the extent by which partial gravity protects against bone loss, if correct assumption?
- What animal models are appropriate to emulate exercise loads in humans?



Discussion Questions (3)

- Is there a requirement for in-flight monitoring of skeletal changes?
- Do you feel that the value of QCT scanning and associated analyses should be standard postflight measurement for skeletal evaluation? A research tool only?
- How critical is the use of MRI technology for muscle volume measurements relative to DXA measurement of muscle mass?



Discussion Questions (4)

- Periosteal expansion is an adaptive response to cortical thinning, as seen with ageing and with QCT hip data (T. Lang) from long duration crew member after R+1 year. (particularly if applied loads can be engineered-out). For a Martian mission, such adaptive changes could occur during in-bound and again during out-bound transits, as well as in multiple long-duration missions. Joyce Keyak's FEA analysis of R+1 year scans is in progress.

How detrimental is it to have wider, more hollow bones?